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Title	Comparative Studies on the Lethal Effects of X-ray, Co60 Gamma-ray, and 14.1 MeV Fast Neutron on Mice
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Citation	日本医学放射線学会雑誌. 23(9) p.1085-p.1093
Issue Date	1963-12-25
oaire:version	VoR
URL	https://hdl.handle.net/11094/16170
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COMPARATIVE STUDIES ON THE LETHAL EFFECTS OF X-RAY, CO^{60} GAMMA-RAY, AND 14.1 MEV FAST NEUTRON ON MICE

By

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X線，Co^{60}ガンマー線，14.1 MeV 速中性子線のマウスの致死効果に関する研究

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（昭和38年10月14日受付）

200 kVp X線，Co^{60} ガンマー線および14.1 MeV 速中性子線の中等度の線量をマウス（ddN系，雌）に照射し，これら3放射線の動物に対する致死効果の差異を比較した．その結果，次のことがわかつた．

1. X線およびガンマー線照射後，30日生存マウスの体重変化曲線は2相性を示した．照射後，5日目頃に第1回，14日目頃に第2回目の体重減少がみられ，減少の度合は後者においてより大きくなる傾向があつた．

2. 中性子線照射マウスは，照射後5日目頃に顕著な体重減少がみられたが，X線やガンマー線照射群で観察された二度目の体重減少は明らかではなかつた．また，5日目頃に現れる体重減少の度合は，中性子線照射群が他の放射線群に比べてはるかに大であつた．

3. 照射後30日間の経日的死亡頻度曲線は中性子線照射群では照射後7日目，X線およびガンマー線照射群ではともに13日目に高いピークを示した．このことから，経日的死亡頻度と体重減少のピークは互いに関係していると推測される．

INTRODUCTION

It is well known that X-ray and gamma-ray are electromagnetic wave radiation and, in general, the biological actions of both radiations are induced by recoiled electrons produced in tissue by Compton effect and photoelectric effect. In contrast with this, it is also well known that neutron is a corpuscular radiation and, when tissue is irradiated by fast neutron, hydrogen nuclei projected in the tissue as recoil protons induce biological effects. In view of these differences in action mechanisms in tissue, it can be readily

assumed that significant differences could exist between the fast neutron and the other two radiations in biological effects. On the other hand, these three radiations distinctly differ from one another in linear energy transfer (LET), and as suggested by Storer and his collaborators[1] it is evident that in mammalian systems the relative biological effectiveness (RBE) of various ionizing radiations depends on the LET.

On the basis of these facts, the present experiment was designed to study the differences in lethal effects on mice during the thirty-day period following exposure to singlre whole-body irradiation of 200 kVp X-ray, Co^{60} gamma-ray and 14.1 MeV fast neutron. For the comparison of lethal effects following such exposures, daily mortality and changes in body weight were studied. A preliminary report has been made by the present author on the lethal effects of X-ray and 14.1 MeV fast neutron[2], and the RBE values for these three radiations as index of $LD_{50/30}$ have previously been reported[3].

MATERIAL AND METHODS

In the present experiment *ddN* female mice (CLEA) were used and the age of mice was 10 weeks and their body-weight was about 23 gm. The irradiated procedure and dosimetry for the three radiations were identical to that described fully in our previous paper (Sawada and Yoshinaga[3]). The basic radiation factors for each of these radiations are as follows:

1. *X-ray* — 200 kVp, 25 mA, HVL: 1.79 mm Cu, Filter: 1.0 mm Cu + 0.5 mm Al, MSD: 65 cm, Dose rate: 10 rad/min, Conversion factor: 0.95 rad/r.
2. *Co^{60} gamma-ray* — 900 curies, MSD: 110 cm, Dose rate: 11 rad/min, Conversion factor: 0.97 rad/r.
3. *Fast neutron* — T (d,n) reaction, Energy: 14.1 MeV, MSD: 5 cm, Dose rate: 4~11 rad/min, Conversion factor: 6.7×10^{-9}rad/n.

RESULTS AND DISCUSSION

I. *Comparison of body-weight curves of the 30-day survivors*

In presenting the body-weight curves of mice after irradiation, the body-weights before irradiation were employed as the basic weights for the irradiated group and non-irradiated group to which changes in weight following irradiation were applied. The daily weight-change rate for the respective groups was obtained by dividing the average weight of the mice surviving per given day by their own average pre-irradiation weight. For 30 days after irradiation all the surviving mice were weighed individually each day.

Several cases of the body-weight curves of the 30-day survivors following exposure to each of the three radiations are shown in Figs. 1, 2, and 3, together with the weight curve of the non-irradiated control mice. The body-weight curves for the X-ray irradiated groups (Fig. 1) and those for the gamma-ray irradiated groups (Fig. 2) are essentially similar to each other. The curves resulting from X- and gamma-ray doses which are approximately equivalent to $LD_{50/30}$ (X-ray: 640 rad, Co^{60} gamma-ray: 870 rad) tend to

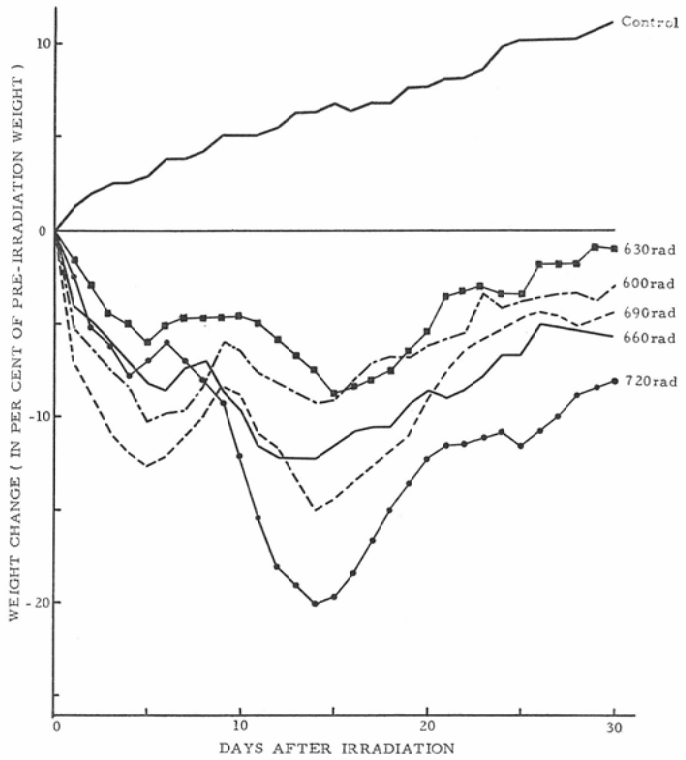

Fig. 1. Weight curves for 30-day survivors in mice exposed to 200 kVp X-ray.

be two peak in nature. Specifically, there is a weight loss peak for the first 4 or 5 days after irradiation, and from the sixth through the ninth day there is either an increase in weight or a decrease less than the first weight loss peak. From the tenth day a progressive weight loss is observed untile the fifteenth or sixteenth day. It was during this latter period of weight loss that the majority of deaths occurred. In general, after irradiation in doses from mid-lethal to high-lethal range (X-ray : 600～720 rad, Co^{60} gamma-ray : 800～940 rad), 30-day survivors lost more weight on the second peak than they did on the first peak. As shown in Figs. 1 and 2, however, the second peak of weight loss in the gamma-ray irradiated groups tends to be greater than that in the X-ray groups.

Fig. 3 shows the body-weight curves for the groups of mice irradiated to various kinds of doses of 14.1 MeV fast neutron. There is a sharp decline in body-weight for at least five days following exposure, but after the sixth or seventh day the surviving mice show a progressive recovery of body-weight. Besides, the weight loss rate during this period appears to be definitely dose dependent. In all dosage groups of the neutron irradiated mice, however, it is difficult to find the second peak in weight loss as observed clearly in X-ray and gamma-ray irradiated groups.

From results of these observations, it is evident that there is an essential difference

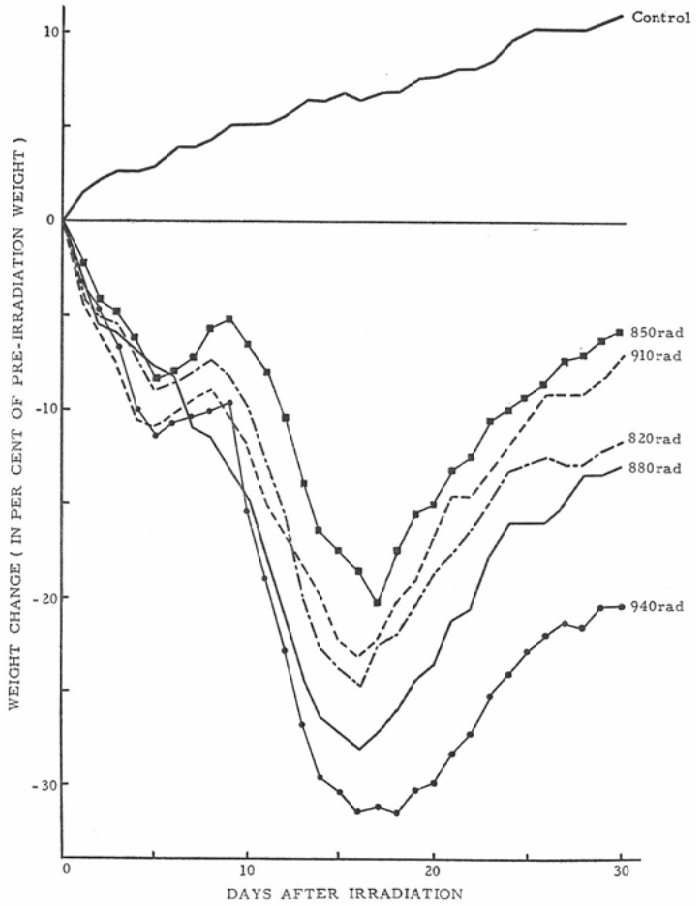

Fig. 2. Weight curves for 30-day survivors in mice exposed to Co^{60} gamma-ray.

between neutron and the other two radiations on the body-weight curves of irradiated mice. Although the three radiations are in good agreement with one another in that they show a peak in weight loss at the fourth or fifth day after irradiation, the peak of the neutron-irradiated mice is of greater magnitude than that of mice exposed to the other two radiations, as shown in the figures. However, the second peak appearing on the fifteenth or sixteenth day is only apparent in the X-ray and gamma-ray irradiated groups.

The two-peak weight curves shown in the present report have been demonstrated with mice and rats after exposure to X-ray or gamma-ray by many authors, such as Lamerton *et al*[4]., Smith and Tyree[5], Chapman[6], Uda and Akamatsu[7], Watanabe[8], Sawada[2] etc. However, the present author exposed mice to sub-lethal doses of X-ray (285 rad and 428 rad) but they did not show a second peak in body-weight loss[2]. A similar finding was reported by Chapman in mice of both sexes[6]. He reported that a correlation existed between the weight loss rate of the second peak and X-ray dosage.

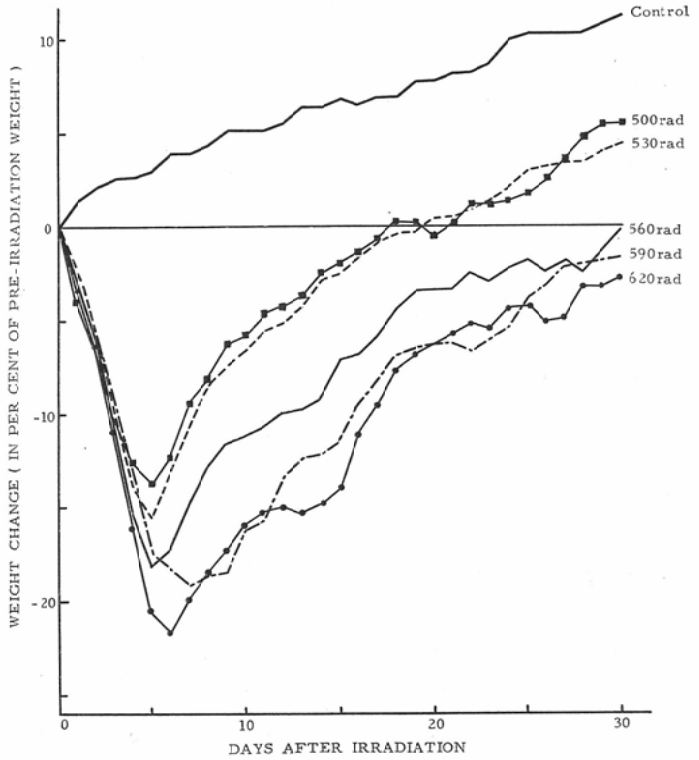

Fig. 3. Weight curves for 30-day survivors in mice exposed to 14.1 MeV fast neutron.

The data concerning body-weight changes of neutron-irradiated animals are limited as compared with those of the X-ray and gamma-ray irradiated animals. In observations of fisssion neutron-irradiated mice, Vogel *et al*[9]. have presented a curve similar to the present results for 14.1 MeV fast neutron in body-weight loss, but the fission neutron-irradiated animals were treated with several protective substances. According to this report there is a sharp peak in body-weight loss on the sixth day after exposure, but after seventh day there is a definite recovery of body-weight without showing the second peak. Nims and Lewis[10] have also reported similar characteristics in weight curves of young rats exposed to thermal neutron. As shown in these results, body-weight changes in neutron-irradiated animals demonstrated a similar pattern for various kinds of neutrons.

It is considered that body-weight curves followed daily observations after exposure suggest a variety of possibilities regarding the mechanism of various factors influencing the course of the acute radiation syndrome. From the many studies conducted in the past, it seems that the first peak in body-weight loss of mice observed at the fifth day after exposure to three radiations developed in most cases by the effect of radiation injury to the gastro-intestinal tract. This damage was especially remarkable in the neutron-irradiated groups. Then, the second peak not observable in the neutron-irradiated mice appeared on the fifteenth or sixteenth day after exposure to the other two radiations as

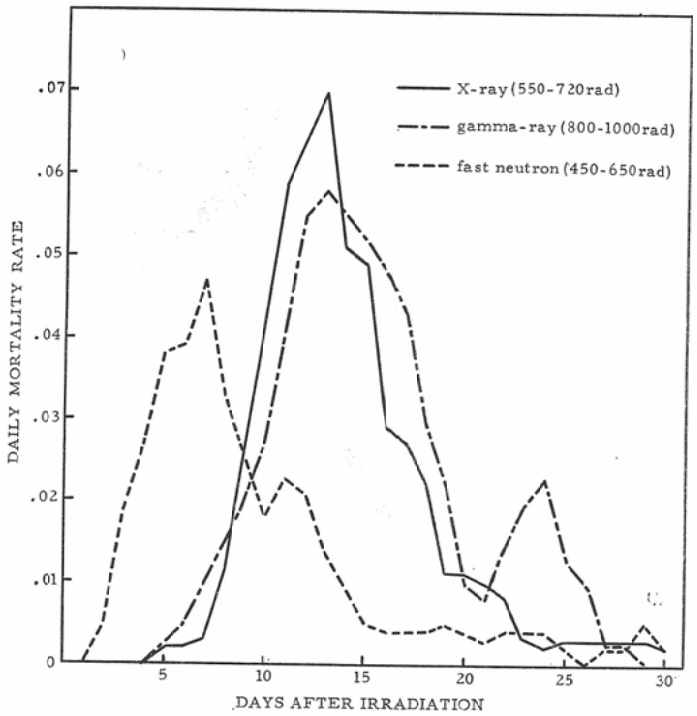

Fig. 4. Comparison of the daily mortality rate in *ddN* mice after exposures to 200 kVp X-ray, Co^{60} gamma-ray, and 14.1 MeV fast neutron. (The daily mortality rate was calculated as a 3-day running average by dividing the number of mice dying during a day by the total number of irradiated mice.)

effect of hematopoietic injury. Therefore, from the body-weight curves alone it may said that neutron may not be as effective as X-ray and gamma-ray in producing hematopoietic injury. Although this can not be elucidated at present, this problem will be considered in greater detail in subsequent experiments.

II. *Comparison of daily mortality rate*

Together with the observation of weight change, it is interesting to examine the daily mortality rate of irradiated mice for 30-days after exposure. In Fig. 4, a comparison is made of the mortality rates after exposure to each of the three radiations. This figure summarizes the time of death of mice from the mortality data of the previous report[3]. The daily mortality rate represented on the vertical axis was calculated as a 3-day running average by dividing the number of mice dying during a day by the total number of irradiated animals.

As can be seen in the figure, it is evident that the mortality rate of mice exposed to the lethal doses of neutron shows a high peak on the seventh day after irradiation and that both of X-ray and gamma-ray irradiated mice demonstrated a pronounced peak on the thirteenth day after irradiation. These results indicate that mice exposed to 14.1 MeV

Table I. Mean survival time (days) of 30-day decedents of *ddN* female mice after single exposure to 200 kVp X-ray, Co^{60} gamma-ray, and 14.1 MeV fast neutron

200 kVp X-ray		Co^{60} gamma-ray		14.1 MeV fast neutron	
Dose (rad)	MST*	Dose (rad)	MST*	Dose (rad)	MST*
720	12.8	1000	15.2	650	7.2
700	16.3	950	14.2	620	8.6
690	12.3	940	13.7	600	7.2
660	15.1	910	15.0	590	13.1
650	19.5	900	16.1	560	14.4
630	13.4	880	16.1	550	12.1
600	16.6	850	15.2	530	10.1
550	14.8	820	18.5	500	8.1
500	—	800	18.4	450	18.5
Mean	14.0	Mean	15.3	Mean	9.6

* MST: Mean survival time (days) of 30-day decedents.

fast neutron die earlier than those irradiated to biologically equivalent doses of X-ray and gamma-ray.

The mean survival time of the 30-day decedents of the groups irradiated to these three radiations is listed in Table 1. In the neutron-irradiated mice considerable differences are noted in the mean survival time in each of the irradiated groups, as indicated in the data. However, from this table it is also apparent that death of the neutron-irradiated mice occurs earlier than that in mice exposed to the other two radiations. On the other hand, X-ray and gamma-ray are very similar to each other with regard to distribution of daily mortality of irradiated mice. According to Vogel *et al*[11]., after irradiation with fission neutrons and Co^{60} gamma-rays, the mean survival time of the 30-day decedents decreased with increasing dosage within the "lethal range", but it was not always so in the present results.

As previously mentioned, most of the deaths occurred during the period of remarkable loss in body-weight. Although some differences exist between the day of the highest mortality and the day of the greatest weight-loss of the 30-day survivors irradiated to the three radiations as shown in Figs. 1~4, it seems certain that these two peaks are closely related with each other. This is very similar to the results observed by Chapman[6] in mice exposed to mid-lethal doses of 2000 kVp X-rays, in which it was during the period of the greatest weight loss (the second week after irradiation) that the majority of deaths occurred.

In a series of articles on the biological effects of fission neutrons and Co^{60} gamma-rays, Vogel *et al*.[9,11,12,13,14,15] have reported that mice exposed to the lethal doses of fission neutrons always show a peak in mortality rate between the 5 th and 10 th day after irradiation, while the peak for gamma-ray irradiated mice occurs at the end of the second week after irradiation. Delihas and Curtis[16] have reported that the peak in death rate for fission neutron-irradiated mice occurred between the 4 th and 8 th day after irradiation,

and the peak for 250 kVp X-ray-irradiated animals occurred between the 10 th and 17 th day. Similar results have been reported by Carter *et al*[17]. with cyclotron neutrons ranging in energy from approximately 3 to about 20 MeV and with 250 kVp X-ray. On the other hand, according to the data obtained by Grahn *et al*[18]., who compared the acute lethal effect on mice exposed to X-rays in the range of 80 to 250 kVp, although the LD_{50} doses increased with decrease in X-ray energy, the mean survival time of the 30-day decedents was nearly the same for animals exposed to X-rays having different kinds of energy. Furthermore, the curve for the daily probability of death of fission neutron-irradiated mice, as reported by Vogel *et al*[15]., is in very good agreement with that for daily mortality rate of 14.1 MeV fast neutron-irradiated animals described in this report in spite of the difference in the kind of neutron quality. These facts strongly suggest that even if the neutrous differ in neutron source, energy and LET, they are very similar to each other in their functional mechanism for biological action.

The early deaths which occur between the 4 th and 8 th day after irradiation seem to be associated with intestinal syndrome as elucidated by Quaster[19]. In contrast with this, the cause of late deaths at the end of the second week after irradiation is considered to be radiation injury to the hematopoietic system. Accordingly, it is not an exaggeration to say that most of the deaths in the neutron-irradiated mice are due to intestinal disturbance, and the main cause of deaths in animals exposed to X-ray and gamma-ray equivalent to $LD_{50/30}$ is related to hematopoietic injury. By a comparative study on such differences in types of death between different kinds of radiations, it may be possible to analyze the cause of radiation injury.

In conclusion, although the 14.1 MeV fast neutron and the two electromagnetic wave radiations, that is 200 kVp X-ray and Co^{60} gamma-ray, differ little from each other in the quantitative comparison based on $LD_{50/30}$, remarkable qualitative differences, that is differences in changes in body weight and daily mortality rate after irradiation, were noted between the former and the latter two.

SUMMARY

From the data obtained with *ddN* female mice exposed to 200 kVp X-ray, Co^{60} gamma-ray and 14.1 MeV fast neutron, these three radiations were compared with regard to their lethal effects on irradiated animals, and the following results were obtained:

1. The body weight curves of 30-day survivors exposed to X-ray and gamma-ray equivalent to $LD_{50/30}$ tended to be two-peak in nature. The first peak in weight loss occurred between the 4 th and 5 th day after irradiation, and the second peak occurred at the end of the second week after irradiation, being in general greater in magnitude especially in the gamma-ray irradiated groups.

2. The neutron-irradiated mice showed a conspicuous loss in body weight on the 5 th day after irradiation, but it was difficult to note the second peak of weight loss as observed in the X-ray and gamma-ray irradiated animals. Their weight loss on the 5 th day after irradiation was greater than mice exposed to X-ray and gamma-ray.

3. In observing the curves of the daily mortality rate during 30 days after irradiation, the neutron-irradiated mice showed a high peak on the 7 th day, while both of X-and gamma-irradiated animals presented a peak on the thirteenth day after irradiatioh. These observations suggest that the peak of weight loss and the peak of daily mortality rate are closely related with each other.

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